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Postexposure Prophylaxis After Possible Anthrax Exposure: Adherence and Adverse Events

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Abstract

Anthrax postexposure prophylaxis (PEP) was recommended to 42 people after a laboratory incident that involved potential aerosolization of *Bacillus anthracis* spores in 2 laboratories at the Centers for Disease Control and Prevention in 2014. At least 31 (74%) individuals who initiated PEP did not complete either the recommended 60 days of antimicrobial therapy or the 3-dose vaccine regimen. Among the 29 that discontinued the antimicrobial component of PEP, most (38%) individuals discontinued PEP because of their low perceived risk of infection; 9 (31%) individuals discontinued prophylaxis due to PEP-related minor adverse events, and 10% cited both low risk and adverse events as their reason for discontinuation. Most minor adverse events reported were gastrointestinal complaints, and none required medical attention. Individuals taking ciprofloxacin were twice as likely (RR =2.02, 95% CI =1.1–3.6) to discontinue antimicrobial prophylaxis when compared to those taking doxycycline. In the event anthrax PEP is recommended, public health messages and patient education materials will need to address potential misconceptions regarding exposure risk and provide information about possible adverse events in order to promote PEP adherence.

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Keywords

Anthrax; Medical management/response; Public health preparedness/response; Adverse reactions; Vaccines

Untreated inhalation anthrax has a mortality rate approaching 100%; even with rapid diagnosis of inhalation anthrax and early initiation of treatment, the mortality rate is near 45%.[1,2] However, it is possible to prevent inhalation anthrax after a known exposure to *Bacillus anthracis* spores by providing individuals with postexposure prophylaxis (PEP), which consists of antimicrobials given orally twice daily for 60 days and 3 doses of BioThrax® (Anthrax Vaccine Adsorbed, AVA) given subcutaneously at 0, 2, and 4 weeks. Prolonged PEP is necessary because inhaled spores can remain dormant for 60 days or longer before germinating, leading to infection long after an exposure event.[3,4] Antimicrobials provide effective protection before the vaccine induces immunity, while the vaccine provides long-term protection from germinating spores beyond the 60 days. Ciprofloxacin and doxycycline are the first-line antimicrobials recommended for PEP by the Centers for Disease Control and Prevention (CDC). Amoxicillin is also an option for individuals exposed to *B. anthracis* strains known to be susceptible to penicillin.[5]

In June 2014, a laboratory incident that involved potential aerosolization of *B. anthracis* spores occurred in 2 laboratories at CDC in Atlanta, Georgia.[6] An initial risk assessment identified 237 individuals who worked in these laboratories from the time that the potential aerosol exposure occurred until the possible exposure events were recognized. PEP was initially recommended for all 237 individuals until individual risk assessments could be performed. This individualized risk assessment evaluated the precise activities and locations of individuals during the potentially aerosolizing procedures.

Potentially exposed individuals were seen in the CDC Occupational Health Clinic (OHC) by a staff physician who reviewed their exposure risk and determined if PEP was indicated. Based on their specific activities and location at the time of potential exposure, 195 of these individuals were determined to have had no risk of exposure to potentially aerosolized *B. anthracis* spores. These individuals, after being on PEP for approximately 4 days, were directed to discontinue by OHC staff and CDC anthrax subject matter experts.

However, for a small group (n =42), potential exposure to aerosolized *B. anthracis* spores could not be excluded, because these individuals had been present in the laboratories when the potentially aerosolizing procedures occurred. For these individuals, their risk was determined to be very low, but not zero, due to their close proximity to the potentially aerosolized *B. anthracis* spores. Therefore, OHC in consultation with CDC anthrax subject matter experts advised these 42 individuals to complete the full 60 days of antimicrobials and the 3-dose vaccine PEP regimen.

Those individuals recommended to receive PEP were given information fact sheets on AVA and that corresponded to the antimicrobial they received. The informational fact sheets explained why the subject matter experts recommended PEP and described how to take the medication and its possible side effects. The PEP administration of AVA required informed

consent as part of the CDC-held Investigational New Drug (IND) protocol, since PEP was not an FDA-approved indication at the time of the CDC laboratory incident. In November 2015, FDA approved the use of AVA for PEP resulting from suspected or confirmed *B. anthracis* exposure, when combined with the recommended course of antimicrobial PEP in people aged 18 through 65 years.

Methods

The Bacterial Special Pathogens Branch (BSPB) in CDC asked that the 42 individuals who OHC had advised to continue PEP participate in a survey regarding PEP choices and possible adverse events. We conducted mid-course (after 30 days of antimicrobials) and end-of-course (after 60 days of antimicrobials) surveys to evaluate adherence to PEP and potential adverse events.

The OHC provided recorded AVA administration under an IND protocol for all vaccinations and made vaccine adherence information available for all 42 participants. The survey protocol was reviewed in accordance with CDC institutional review policies for research involving human subjects, and it was determined that this survey did not meet the definition of research subject to regulation under 45 CFR 46.102(d).

BSPB removed all personally identifiable information from survey material and stored information in a secure location. PEP was given without regard to survey participation. BSPB conducted all interviews by phone during work hours. BSPB assigned each participant to an interviewer who performed both interviews. BSPB recorded data on paper survey forms, entered data into Microsoft Access in duplicate, and then compared data for errors. Risk ratios were calculated using SAS statistical software.

Results

The median age of survey participants was 37 years (mean 39 years), and 52% were female. The potentially exposed staff included 17 (40%) research scientists, 15 (36%) laboratory technicians, and 10 (24%) facility maintenance personnel. None of the potentially exposed staff developed anthrax.

Overall, 28 (67%) participants declined to complete the full vaccination series; 20 participants declined the first vaccine dose; an additional 6 declined the second dose; and 2 more declined the third dose. Low perceived risk was the most common reason provided by individuals who declined initial vaccine (13/16, 81%) and who stopped vaccination early (4/8, 50%). The second most common reason provided was either fear of adverse events for declining initial vaccine (5/16, 31%) or experienced adverse events for stopping vaccine early (3/8, 38%).

Information regarding antimicrobial adherence was available for 29 (69%) individuals who agreed to participate in the mid-course survey and 18 (43%) individuals who completed the end-of-course survey. Of the 29 individuals who responded to the mid-course survey, 28 (97%) reported starting the antimicrobial PEP course; however, 15 (52%) reported discontinuing it after 4 weeks. Only 6 (33%) of the 18 who responded to the end-of-course

survey reported completing the 60-day antimicrobial component of the PEP course. Two individuals who had discontinued PEP at the mid-course survey stated that they restarted and finished the 60-day antimicrobial PEP course.

Low perceived risk was the most common reason provided by individuals who stopped antimicrobial PEP early (9/14, 64%) followed by experiencing adverse events (5/14, 35%). With both antimicrobial and vaccine adherence considered, at least 31 (74%) individuals who initiated PEP did not complete the full recommended PEP regimen. No demographic differences were seen between those individuals who were adherent or were not adherent with the recommended PEP.

Over the 60-day survey period, 28 people were prescribed ciprofloxacin; 17 people were prescribed doxycycline, 4 of whom were initially prescribed ciprofloxacin and later changed to doxycycline due to adverse events. The most commonly reported adverse event associated with antimicrobial use was gastrointestinal symptoms (Table 1). While we found no significant difference in the number of people who reported side effects after taking doxycycline (69%) versus ciprofloxacin (67%), all individuals who completed their antimicrobial prophylaxis took doxycycline. Based on information from the mid- and end-of-course surveys, of the 17 individuals taking ciprofloxacin, 88% (15) stopped the antimicrobial course early. In contrast, 44% (7) of the 16 taking doxycycline stopped the antimicrobial course early. Overall, those taking ciprofloxacin were twice as likely to discontinue the antimicrobial course as those on doxycycline (RR =2.02, 95% CI =1.1–3.6).

Some individuals who stopped PEP provided responses to open-ended questions suggesting that they did not understand the concept of PEP. Participant comments suggested they mistakenly thought they were adhering to the PEP recommendations. For example, 3 people stated that they chose to take antimicrobials instead of vaccine because they believed that both were unnecessary, and 2 people mentioned they would start PEP if they or others associated with this laboratory incident developed anthrax.

Discussion

Most individuals present during the potential aerosolization of *B. anthracis* spores in this laboratory incident whom OHC determined to have low but not zero risk of developing inhalation anthrax did not complete combined PEP. The actual number of CDC contractors and staff who did not complete PEP might be even higher, as we could not assess antimicrobial adherence in those who did not participate in the survey. Many of the survey participants discontinued PEP after they made an individual determination that their risk for inhalation anthrax was low.

As part of the laboratory investigation, the level of risk could be refined based on activities and location because of the known place and method of exposure. The level of exposure of individuals present during the event reported here was low, but not zero. Review of the laboratory procedures that resulted in the potential exposure suggest release of only small, if any, amounts of viable spores. In addition, environmental sampling of the area did not detect any viable spores. Together, these data support that any potential risk was low.

The people involved in this event were notified by OHC that their risk of potential exposure to *B. anthracis* spores was low. Hence, it could be argued that these individual decisions were informed by their particular risk tolerance for what they deemed to be extremely low risk. The low risk of exposure and knowledge of anthrax by many in the exposed laboratory staff in this event potentially limits the applicability of these findings to any high-risk event with a broad dissemination of a concentrated dangerous pathogen in the general population. Nonetheless, important observations were made regarding PEP choices as they relate to perceived and actual risk, side effect profiles of the medication, and familiarity with PEP recommendations. During a mass exposure event, the risk of exposure would almost certainly vary. For those with exposures similar to hospitalized or fatal cases of inhalation anthrax, perceptions about personal risk could change, thus motivating them to adhere to PEP. However, those incubating anthrax who perceive a lower risk of exposure might forego PEP.

It is important to understand the reasons why individuals discontinue PEP. Statements from survey participants suggest a lack of understanding regarding the role of PEP in preventing disease, and, as such, public health messages regarding the role of antimicrobials and vaccine in PEP are important to increase adherence. A previous study[7] that assessed anthrax PEP adherence following the 2001 anthrax incident when *B. anthracis* spores were sent through the US Postal Service[8] found that 56% of those considered at risk of exposure to aerosolized *B. anthracis* spores discontinued their PEP course, even in the context of a bioterrorism-related anthrax event. This study found a strong association between perceived risk and PEP adherence.[7] Despite receiving a recommendation to take PEP, most individuals who completed the survey indicated that they determined they were not at risk and made the individual decision to either not initiate PEP or discontinue PEP early. The results of testing the environmental samples in the laboratory revealed no growth of *B. anthracis,* and this may have been an additional factor informing the individuals' decisions. Results from environmental sampling would also play a role in decisions on individual risk assessment in a larger event.

Survey participants reported that the second most common reason for discontinuing PEP was prophylaxis-associated adverse events. This is consistent with PEP adherence after the 2001 anthrax incident,[8] where study participants cited adverse events as the most common reason for discontinuing PEP, with 43% of study participants citing adverse events and 7% citing fear of long-term adverse events.[7] The adverse events profile reported by participants in this survey is consistent with known side effects of these medications.[9,10] While serious adverse events associated with anthrax PEP are very rare, mild adverse events are common for fluoroquinolones,[11] doxycycline,[12] and AVA.[13] Both studies demonstrate that adverse events, even those considered minor and common, are cited reasons for discontinuation of PEP.

Although our survey does not show a statistically significant difference in the number of adverse events experienced by those on ciprofloxacin compared to those on doxycycline, it does show that individuals on ciprofloxacin were twice as likely to stop antimicrobial prophylaxis as those on doxycycline. Another study comparing adverse events during long-term treatment with ciprofloxacin or doxycycline showed that long-term use of these

antimicrobials appears safe. However, ciprofloxacin did show a higher risk of adverse events over the first 28 days. This increased risk was not seen after 28 days.[14] This difference in the adverse event rate between ciprofloxacin and doxycycline might relate to the likelihood of discontinuation of PEP and should be investigated further. If validated, this difference might be a consideration when prescribing PEP and when public health agencies develop messages surrounding PEP adherence.

In summary, most people in this survey did not complete the recommended course of PEP due to a low perceived personal risk of developing inhalation anthrax or because they experienced adverse events. Although in these cases the perceived low risk was likely accurate, the findings from this survey and the 2001 anthrax incident study[7] suggest the need for effective risk-benefit communication strategies to address PEP adherence in situations where exposure risk could be perceived as low or very low. This survey also suggests the need for messages that clearly convey how PEP works, why it is critical to take the medicines and vaccine as directed, and step-by-step guidance on how to follow the recommendations. Understanding the components of any individual's risk tolerance and risk assessment thought process is also important.

The results reported here indicate that public health agencies must anticipate changes to risk categorization during an anthrax incident and that mild adverse events will be common. Both could influence people's perceptions of how important it is for them to continue taking PEP. While planning for a response, evidence-based public health messages and communications strategies should address these challenges.[15]

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Table 1

Adverse events related to postexposure prophylaxis following a laboratory incident involving potential aerosolization of *Bacillus anthracis* spores, Centers for Disease Control and Prevention in 2014

	Any Antimicrobial No. (%)	Ciprofloxacin No. (%)	Doxycycline No. (%)	Changed[a] No. (%)	Vaccine No. (%)
Number potentially exposed	48	28	13	7	28
Any side effect	32 (67)	19 (67)	9 (69)	6 (86)	24 (86)
Nausea	18 (38)	9 (32)	6 (46)	3 (43)	0
Diarrhea	9 (19)	5 (18)	1 (8)	3 (43)	1 (4)
Stomach cramps	7 (15)	2 (7)	3 (23)	2 (29)	0
Pain in muscles	6 (13)	4 (14)	0	2 (29)	5 (18)
Rash	6 (13)	2 (7)	2 (15)	2 (29)	3 (11)
Difficulty sleeping	5 (10)	4 (14)	0	1 (14)	2 (7)
Dizziness	5 (10)	3 (11)	1 (8)	1 (14)	1 (4)
Fatigue	5 (10)	1 (4)	1 (8)	3 (43)	7 (25)
Headache	5 (10)	3 (11)	0	2 (29)	6 (21)
Pain in extremities	4 (8)	1 (4)	1 (8)	2 (29)	3 (11)
Pain swallowing	3 (6)	2 (7)	0	1 (14)	1 (4)
Vomiting	3 (6)	1 (4)	2 (15)	0	0
Bruising and bleeding	2 (4)	1 (4)	1 (8)	0	0
Difficulty breathing	2 (4)	2 (7)	0	0	0
Irregular heartbeat	2 (4)	0	1 (8)	1 (14)	0
Moodiness	2 (4)	0	0	2 (29)	1 (4)
Vision problems	2 (4)	1 (4)	0	1 (14)	2 (7)
Swelling of neck	2 (2)	1 (4)	0	0	1 (4)
Limited motion of arm	0	0	0	0	9 (32)
Tender at site	0	0	0	0	21 (75)

[a]Individuals who changed antimicrobials during prophylaxis and therefore were unable to attribute their side effects to a specific medication.